Chapter 1
Academic Public Private Partnership Program (AP4): Overview

Background

Cancer is the second leading cause of death in the United States, where it is responsible for one of every four deaths. In the next 50 years, the number of Americans diagnosed with cancer each year is expected to double, from 1.3 million to 2.6 million. The National Institutes of Health (NIH) estimates that the overall annual cost of cancer was approximately $171.6 billion in 2002, including health expenditures and lost productivity due to illness and premature death.

Since 1955, when the National Cancer Institute (NCI) established a testing program for discovering and developing drugs to treat cancer, the U.S. Food and Drug Administration (FDA) has approved 66 anticancer agents (excluding vaccines and other biologics). But only a few of these drugs are cancer-specific, molecular-target-directed agents. The rate of New Drug Applications (NDAs), approval of which is necessary for the sale of newly discovered agents to the public, has decreased in the last 10 years, in spite of advances in chemistry, computer modeling, microtechnology, and molecular biology, which had been expected to have the opposite effect. In fact, in 2001, the entire multibillion-dollar pharmaceutical industry launched only a single chemical agent against a novel target.

As a result, a widely recognized need exists to expedite the clinical development and regulatory approval of new cancer therapies. Discovering and developing a cancer drug to the point at which an NDA is filed is estimated by the pharmaceutical industry to cost up to $800 million and require up to 15 years of research, clinical trials, and marketing.

At the same time, scientific breakthroughs have revealed that many, if not all, human cancers can be classified into genetic subtypes. The numbers of patients with each of the genetic defects that have been identified are relatively small. Therefore, the population of patients who may benefit from a new rationally designed targeted drug or diagnostic or imaging technology is also likely to be quite small and thus of limited interest to large pharmaceutical and biotechnology companies.

The NCI has several programs that support the development of cancer therapies, but none addresses the need for multidisciplinary expertise involving academic research centers, pharmaceutical and biotechnology companies, nonprofit agencies, and government entities focused on the rapid development of new cancer therapies. The NCI's Division of Cancer Treatment and Diagnosis (DCTD) investigator-initiated (R01) grants are generally designed to support hypothesis-driven research in anticancer drug discovery, but are not focused on the preclinical development of meritorious and novel interventions. Molecular Targeted Drug Discovery (MTDD) grants are treatment directed, but based at a single academic or small business research entity and not required to be multidisciplinary. The National Cooperative Drug Discovery Groups (NCDDG) support innovative multidisciplinary approaches to the discovery of new, synthetic, or natural-source-derived anticancer drugs. But while the active participation of industry and nonprofit research institutions is encouraged, it is not required. Moreover, while these groups can alter research projects, they must obtain NCI approval to do so.

The NCI developed the Academic Public Private Partnership Program (AP4) in 2003 to bring together the multidisciplinary expertise needed to discover new, more effective treatment, diagnostic, and prevention interventions for cancer; shorten the time required to bring these new interventions to clinical trials; and reduce the financial risks of cancer intervention discovery and development for pharmaceutical and biotechnology companies. AP4 creates partnerships among academia, industry, nonprofit institutions, and government entities to conduct research on novel cancer therapeutic, prevention, diagnostic, and imaging interventions.

Purpose

Unlike the DCTD R01 projects, the AP4 centers include the preclinical development of novel interventions. In contrast to the MTDD grants, AP4 centers are multidisciplinary partnerships between academic or nonprofit research centers, pharmaceutical and biotechnology companies, and government entities. In addition, the AP4 centers have an advantage over the NCI NCDDGs by being highly flexible in discontinuing some research projects while adopting new projects with the consent of the center steering committees, without requiring approval from the NCI or a peer-review panel.

This last feature makes the initiative particularly attractive to industrial partners who use the "fail fast" approach to intervention discovery, which recognizes the value of discontinuing research on compounds early, during preclinical development, once it is clear that they will ultimately fail. This flexibility also makes AP4 centers attractive partners for nonprofit organizations with a strong interest in the rapid discovery and development of new interventions directed toward orphan diseases. Vesting decision-making power in the steering committee allows each center to react swiftly to new trends and new information in relevant research fields that continue to experience paradigm shifts at increasingly rapid rates.

AP4 represents a novel approach to the funding of preclinical anticancer intervention discovery and development. Although elements of the program exist within the NCI portfolio, none of the institute's other programs encourages the establishment of long-term multidisciplinary relationships or allows multiple industrial partners to stimulate and fund academic research in conjunction with nonprofit organizations. The inclusion of a steering committee of center partners with the authority to determine project viability and decide whether to continue, cease, or add projects is also a unique and enabling feature of AP4 centers. The inclusion of multiple partners from the pharmaceutical, biotechnology, and nonprofit sectors ensures that AP4 center projects are of interest to industry and patient advocate organizations.

The research of the AP4 partnerships takes advantage of the latest discovery and development technologies and uses a multidisciplinary approach to focus on orphan cancers (those that affect fewer than 200,000 people per year in the United States) or biologically defined subsets of more common tumor types. The research occurs at academic centers or at nonprofit institutions that have formal relationships (such as joint faculty appointments) with degree-granting academic institutions or that have identified a degree-granting institution as a partner, with advice and support from NCI as well as industrial, academic, nonprofit, and other government partners. The goal of the research, which may begin as basic research, is to generate novel interventions for human clinical trials.

AP4 brings together the basic research skills of academic and nonprofit groups, the scientific and marketing expertise of industry, the resources and interests of disease-oriented charities, and the administrative support, resources, and years of discovery and development expertise of the NCI. At the same time, AP4 provides the next generation of researchers with experience and training unavailable elsewhere in multidisciplinary, collaborative, discovery-oriented research. The resulting public-private partnerships will advance our basic knowledge of the molecular biological events that lead to cancer and apply that knowledge to the development of novel cancer interventions.

AP4 Features

Figure 1-1: Possible indicators of success for the AP4 program*

Administrative and financial:
- Number of AP4 centers in operation.
- Total AP4 budget.
- Average direct funding per center per year.
- Percentage of AP4 center funding provided by the NCI.

Model generalizability:
- Diverse cancers addressed by AP4 research projects.
- Implemented by small- and medium-sized institutions and a variety of departments.

Model impact:
- Number of institutions involved in AP4 centers.
- Number of investigators actively involved in conducting research within AP4 centers.
- Number of industrial memberships in AP4 centers.
- Number of academic/nonprofit memberships in AP4 centers.

Impact on investigators:
- Number of papers published by investigators based on AP4 research.
- Number of dissertations supervised to completion by faculty members based on AP4 research.
- Number of investigator awards from academic and professional associations based on AP4 research.

Impact on students:
- Number of graduate and undergraduate students actively involved in research within AP4 centers.
- Number of students involved in AP4 research who complete their degrees.
- Number of students involved in AP4 research who pursue additional education or jobs related to anticancer intervention development.
- Number of papers published by students based on AP4 research.
- Number of student awards from academic and professional associations based on AP4 research.
- Number of job offers to students involved in AP4 research.
- Rating of their educational experience by students involved in AP4 research.

Impact on industry:
- Average number of disclosures and patents produced by each center.
- Annual follow-on research support per industry partner and AP4 center, and for the entire AP4 initiative.
- Number of members reporting a knowledge or technology transfer success.
- Number of commercial products and processes developed as a result of AP4 research.

Impact on academic institutions, nonprofit organizations, and government agencies:
- Number of new interventions (including diagnostic tools) available for patients.
- Number of new interventions directed at "orphan" diseases.
- Length of time from discovery to clinical trials.

*Adapted from Gray and Walters, p. 11.

Rather than working on small-scale, narrowly defined problems within a single discipline, AP4 center investigators conduct research on issues that are both scientifically important and relevant to the cancer research community. While investigators often design research programs around personal interests, in AP4 centers they develop projects in collaboration with industry and other

partners. Instead of working on their own, center investigators carry out AP4 projects in multidisciplinary teams with members from other institutions. Although sharing knowledge through publication is an important objective of investigators in AP4 centers, they also recognize the economic and social value of their research and take responsibility for transferring the resulting knowledge and technology to industry and government, so these can ultimately reach and benefit patients.

At the same time, AP4 center pharmaceutical and biotechnology partners do not use AP4 centers as a low-cost, convenient means of solving short-term problems. Instead, these companies make long-term commitments to AP4 centers to support fundamental research in collaboration with other companies that may be competitors. Although knowledge, technology transfer, and commercialization of research results remain the primary objectives of pharmaceutical and biotechnology partners in AP4 centers, they recognize the importance of publishing findings from the centers and training investigators who will develop the next generation of anticancer therapies.

Disease-specific advocacy organizations contribute to NCI programs, including the AP4 centers, by offering advice and planning assistance based on their expertise, usually in a specific cancer type, and the consumer perspective. In the AP4 centers, charitable agencies can help reduce drug development time by directing patients to clinical trials that arise from successful AP4 intervention projects, and by providing grants and other resources to support the work of the centers.

Many state government agencies have established cancer control programs to support innovative and creative cancer research in their states, particularly on the causes, prevention, detection, and treatment of cancer. These programs are often supported by tobacco settlement funds and taxes, a portion of which can be directed to AP4 programs. State government agencies also share data from their cancer registries with AP4 centers and help recruit patients for clinical trials from the cancer screening programs they sponsor.

Each AP4 center includes:

- A director located at a U.S. university or nonprofit, who conceives of the idea, applies for and coordinates the planning grant effort, and, if successful in the subsequent center application, coordinates all aspects of the center. The center director consults with center partners to define a research agenda focused on shared research interests, needs, and opportunities.
- Multidisciplinary participation from such fields as chemistry, biology, immunology, and screening technologies.
- Research projects of interest to the cancer research community, the goal of which is to culminate in interventions.
- Biotechnology, pharmaceutical, academic, nonprofit, and/or state and local government partners who are the partners of each center and who contribute financially to center operations.
- A steering committee with representatives of each partner institution that approves ongoing activities and recommends new projects, responding to current, evolving

opportunities. The NCI program coordinator serves as a nonvoting member of this committee.

- A membership agreement that serves as a formal operations document and specifies the center's structure and policies. It addresses how the center is governed, as well as the management of prospective intellectual property issues, publication procedures, and membership fees and rights. Different centers may have substantially different agreements.
- Development of scientific expertise in research relevant to cancer intervention and discovery and development at the academic level.
- A strong research team capable of developing and operating an AP4 center.
- Annual formal evaluations of the partnership by an independent evaluator who provides survey and analysis information to center directors and partners to continually improve the center. The evaluator is responsible for preparing, on an annual basis, a review of center activities, including:
  - Status of collaborations.
  - Participant satisfaction with center activities.
  - Management and operation of the center.
  - Exit surveys from partners who have withdrawn from the center.

NCI provides each AP4 center with:

- Direct access to the development contract resources of the NCI's Developmental Therapeutics Program (DTP)—including applied tasks such as manufacturing issues (e.g., bulk synthesis), pharmacology, toxicology, and formulation research—for promising lead compounds approved by the center steering committee. Criteria for access to DTP resources are the same as those used to evaluate the NCI's other drug development opportunities <http://dtp.nci.nih.gov/docs/ddg/ddg_descript.html>.
- Investigational New Drug (IND) filing assistance for an NCI-based or principal-investigator-directed clinical trial is provided on a case-by-case basis. This may involve assistance in putting together INDs held by the originating center or assumption of the IND if the agent is to be studied more broadly in NCI's early clinical trials groups.
- Access to NCI resources, including compound samples and sets, biologics, natural product extracts, high-throughput screening for cancer and AIDS, Web-accessible data and tools, and research expertise and advice.

The ideal AP4 center is based at an academic or nonprofit center and includes biotechnology, pharmaceutical, academic, nonprofit, and disease-oriented charity partners, each with an interest in translating novel anticancer therapeutic, prevention, diagnostic, and/or imaging interventions from the laboratory to the clinic. Each center partner may focus on a different functional area of the intervention discovery and development process. Alternatively, partners may agree to pool their resources to support one aspect of a discovery and development program; the actual roles and goals of each center's partners are articulated by the center director and included in the membership agreement. Each center begins with at least three collaborative research projects that are designed to develop a new anticancer therapeutic, preventive, diagnostic, or imaging agent of interest to the partners. The research approaches used may focus on underserved malignancies and take advantage of the latest technologies, allowing the center to discover and develop

molecules and other intervention technologies in a new way. Existing partnerships may apply for an AP4 center planning grant, provided that the initial three projects are new to the partnership.

The center's steering committee decides whether to continue current projects or start new ones. Project management is dynamic; in the lifetime of a center, funds may be shifted freely from one project area to another at the discretion of the steering committee and according to processes outlined in the center agreement. The AP4 effort thus differs fundamentally from traditional center (P01) and other grant programs funded by NCI, in which defined projects are expected to continue for the life of the grant.

Each center must submit an annual report, which is used to assess annual performance, to the NCI program coordinator. Each report should address major accomplishments, operating budget, evaluation results, research goals, and processes used to communicate with center partners.

AP4 centers with a combined partnership investment of at least $450,000 per year receive $600,000 (direct costs) in each of the first 3 years from the NCI. Other centers receive $450,000 per year (direct costs) in Years 1–3 from the NCI, with a *minimum* of an additional $300,000 per year (total) from center partners. Funding in Year 4 is 75% of the initial direct cost level, and 50% of the initial direct cost level in Year 5, to encourage centers to acquire additional contributing partners and prepare to become self-sustaining.

The NCI expects that AP4 centers that are successful in meeting their goals will be able to compete for a second 5-year award of $100,000–$200,000 (direct costs) per year. After 10 years, centers that continue to operate will be fully supported by industrial, nonprofit, other (non-NIH) federal, and/or state and local government partners.

Figure 1-2: NCI funding (direct costs) for AP4 centers

	NCI Contribution (Direct Costs)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Years 6–10**
Centers with at least $450,000 per year in non-NCI funding.	$600,000	$600,000	$600,000	$450,000	$300,000	$100,000–$200,000
Centers with at least $300,000 per year in non-NCI funding.	$450,000	$450,000	$450,000	$337,500	$225,000	$100,000–$200,000

Planning Grant

The NCI assists in the formation of AP4 partnerships by offering a 1-year, $50,000 (direct costs) planning grant. Proposed AP4 center directors use the planning grant to study the feasibility of developing the pharmaceutical/biotechnology/nonprofit/academic interaction necessary to establish or significantly expand existing partnerships and determine whether to apply for an

AP4 center grant. During the planning grant period, the potential AP4 center plans and holds a meeting of potential partners to explore opportunities, defines how intellectual property issues will be handled, and establishes a research plan. Applications for the planning grants are competitive and peer reviewed.

The ideal planning grant arises from an academic or nonprofit center with a clear track record of funded research in cancer biology that has identified an overall theme and/or disease to study. Additionally, the center has a range of potential partners in developing the program and resources from the center's home institution. Letters of interest in a potential AP4 center from at least two potential partners are required. These letters are not viewed as full or formal commitments, but as a basis for further discussion. The NCI recognizes that the final AP4 center application may contain commitments of a subset of these or additional potential partners. Only planning grant recipients are eligible to submit an application for an AP4 center.

Organization of this Handbook

This handbook is designed to help you apply successfully for an AP4 planning grant, and then for an AP4 center grant. It is divided into two sections, with the following chapters:

Section 1: Planning an AP4 Center

1. *AP4 Overview*: The AP4 initiative, including its purpose and features, and the planning grant.
2. *The Planning Grant Application*: Planning grant application content and format, feasibility study, letter of intent, preparing the planning grant application, and the criteria used to review applications.
3. *The Planning Year*: Goals of the planning year and stages of planning, recruiting center partners, and the partners meeting.
4. *Strategic Planning*: The goals of strategic planning, the strategic planning process, and the format and content of a strategic plan.
5. *The Center Proposal*: Requirements of the AP4 program, funding mechanism, content, format, and review criteria of the application for an AP4 center.

Section 2: Managing an AP4 Center

6. *Center Administration*: Center personnel, research personnel, steering committee, governance, policies, and procedures.
7. *Selecting AP4 Center Research Projects*: Reviewing proposals for research projects, roles of partners in developing project ideas, research project management and evaluation.
8. *Communications*: Semiannual meetings, formal reporting, and internal and external communications.
9. *Evaluation of the AP4 Center and the Role of the Center Evaluator*: Steps in the evaluation process, center partner and investigator surveys, and responsibilities of the AP4 center evaluator.

References

American Cancer Society. *Cancer Facts and Figures 2003.* Available at: <http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf>. Accessed May 9, 2003.

Gray D.O., Walters S.G. *Managing the Industry/University Cooperative Research Center: A Guide for Directors and Other Stakeholders*. Columbus, OH: Battelle Press, 1998.